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Optimizing Strategies to Assess Mucosal Healing in Patients With Crohn's Disease

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Abstract: In the past 5 years, the goal for the treatment of Crohn's disease has evolved from managing patient-reported symptoms to the new paradigm of treat to target, a strategy that involves treating the target of the underlying inflammation by means of tight control. Mucosal healing is an important clinical endpoint that correlates with fewer surgeries and hospitalizations, as well as higher quality of life. Colonoscopy is the gold standard for measuring mucosal healing, but has limitations involving bowel preparation quality, the need for serial examinations to compare degrees of inflammation, and the procedure's relative invasiveness. Patients with Crohn's disease prefer blood-based tests vs stool-based tests. However, the currently available noninvasive biomarkers, such as C-reactive protein and fecal calprotectin, are associated with several limitations. The recently validated Prometheus Monitr Test consists of 13 biomarkers that represent 6 biologic pathways involved in the process of mucosal healing and mucosal homeostasis. The test provides an endoscopic healing index (EHI). Data suggest that the EHI score provided by the Prometheus Monitr Test could be used as a noninvasive surrogate for accurately assessing mucosal endoscopic disease activity in patients with Crohn's disease, regardless of the disease location.

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Reference to mucosal healing in these articles means endoscopic healing.

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Monitoring of Mucosal Healing in Crohn's Disease: A Review of the Data

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The Role of Mucosal Healing in Crohn's Disease

Mucosal healing has become an important clinical target for patients with Crohn's disease.¹ Among these patients, mucosal healing correlates with reduced needs for surgery and hospitalization, as well as maintenance of a high quality of life.²⁻⁴ However, the gold standard for measuring mucosal healing—colonoscopy—has limitations involving bowel preparation quality, the need for serial examinations to compare degrees of endoscopic disease activity, and the procedure's relative invasiveness.^{1,5} Because of these limitations, it is difficult to rely upon colonoscopy for serial monitoring of endoscopic disease activity and treatment response in routine clinical practice.

Description of the Prometheus Monitr Test

The Prometheus Monitr Test consists of 13 serum protein biomarkers that represent 6 biologic pathways involved in the process of mucosal healing and mucosal homeostasis (Figure 1).⁶ These biomarkers were selected through an iterative process, which involved correlating expression of the particular biomarker against endoscopic disease activity. During the selection of these biomarkers, multiple signaling pathways were considered. As a result, the final model includes biomarkers that are not limited to inflammatory markers only that are traditionally associated with endoscopic disease activity. They include biomarkers from the angiopoietin and matrix metalloproteinases families, as well as carcinoembryonic antigen-related cell adhesion molecule 1, C-reactive protein (CRP), serum amyloid A1, interleukin 7, transforming growth factor α , vascular cell adhesion molecule 1, and extracellular matrix metalloproteinase inducer.⁶ Data were modeled using logistic regression, and the results were reported as an endoscopic healing index (EHI) score, which is graded on a scale of 0 to 100.⁶

Information regarding the development and vali-

ation of the EHI model and the Prometheus Monitr Test was published in *Gastroenterology* by D'Haens and colleagues in 2020.⁶ At a cutoff score of 20, the sensitivity of the EHI was 83.2% for excluding endoscopically active disease, with a specificity of 36.6% (Figure 2). At a cutoff score of 50, the sensitivity of EHI was 30.1% for excluding endoscopically active disease, with a specificity of 87.8%. For EHI cutoffs of at least 20 but less than 50, specificity steadily increased as the scores approached 50, which indicates a higher likelihood of active disease.

Clinical Studies of the Prometheus Monitr Test

The study by D'Haens and colleagues evaluated serum samples from 589 adult patients with Crohn's disease who were divided into 3 cohorts: a training set and 2 validation sets.⁶ All of the validation samples were obtained ± 45 days of endoscopy. Approximately 66% of the samples were collected on the same day as the endoscopy, including 44.7% of validation cohort 1 and 96.4% of validation cohort 2. Among the samples in the training cohort, 90.1% were obtained ± 45 days of endoscopy, including 43.9% that were collected on the same day as the procedure. For the 2 validation cohorts, endoscopic remission was defined as a total Simple Endoscopic Score for Crohn's Disease (SES-CD) of 2 or lower and of 1 or lower in each intestinal segment. In the training cohort, endoscopic remission was defined as a total Crohn's Disease Endoscopic Index of Severity (CDEIS) score of less than 3. The study defined active disease in 3 ways: a CDEIS score of 3 or higher; an SES-CD score higher than 2; or an SES-CD score of 2, if only 1 segment had a score of 2 and the remaining segments had a score of 0.

The training cohort consisted of 278 patients with Crohn's disease, who had made 335 endoscopy visits.⁶ Patients were drawn from the STORI (Stop Infliximab in Patients With Crohn's Disease) clinical trial, as well as studies conducted at the University of Padua in Italy,

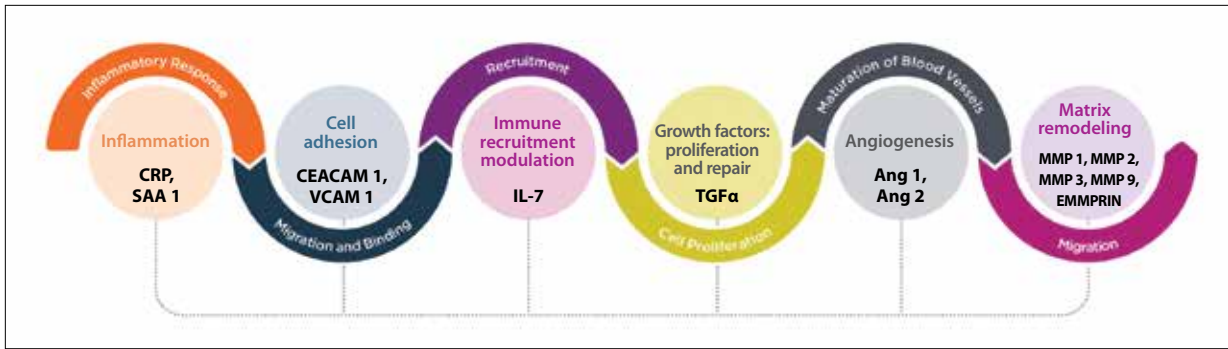


Figure 1. Biomarkers in the Prometheus Monitr Test. These biomarkers provide insight into the extent of mucosal damage, the function of repair pathways, and other associated factors.

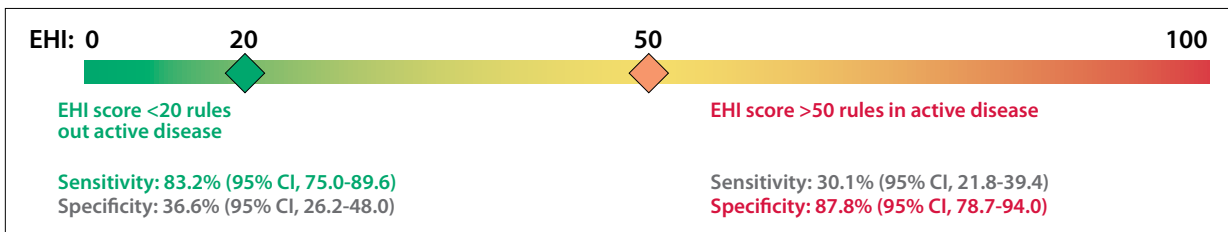


Figure 2. The endoscopic healing index score ranges from 0 to 100. Sensitivity and specificity are shown for the higher and lower ranges. EHI, endoscopic healing index. Data from D’Haens G et al. *Gastroenterology*. 2020;158(3):515-526.e10.⁶

the University of California San Diego, and Mount Sinai Hospital in Toronto, Canada. The median age of patients in the training cohort was 30 years (interquartile range, 24.9-40.0), and 54% were male. The median duration of disease was 4 years (interquartile range, 3.0-12.5).

Data from the training cohort were used to develop the EHI model, which was trained against endoscopic disease activity (CDEIS).⁶ The researchers used a multiple logistic regression method to predict endoscopic activity. The EHI was based on a scale of 0 to 100 arbitrary units measuring endoscopic disease activity. A higher score corresponded to more severe disease.

The performance of the EHI score was validated with 2 cohorts.⁶ Validation cohort 1 included 116 patients from the TAILORIX trial (Tailored Treatment With Infliximab for Active Crohn’s Disease). Patients in this cohort were treated with infliximab plus an immunosuppressant. The mean age of validation cohort 1 was 30.2 years (interquartile range, 22.4-45.2), which was similar to the training set. Only 40.5% of the patients were male, a significant difference compared with the rate of 54% in the training cohort ($P=.02$). These patients provided 275 serum samples. For validation cohort 1, the investigators calculated an area under the receiver operating characteristic curve (AUROC) of 0.962 (95% CI, 0.942-0.982) for EHI and 0.876 (95% CI, 0.835-0.916) for CRP for distinguishing active disease from endoscopic remission (Figure 3). The

AUROC was 0.950 (95% CI, 0.925-0.976) for EHI and 0.923 (95% CI, 0.884-0.962) for fecal calprotectin (Figure 4). At an EHI cutoff of 20 or lower, the sensitivity for excluding endoscopic disease activity was 97.1% (95% CI, 93.7%-98.9%). CRP 5 mg/L sensitivity was 44% and 100% for fecal calprotectin. At an EHI cutoff of 50, the specificity for excluding active disease was 100% (95% CI, 94.9%-100.0%). CRP 5 mg/L was 97% and 63% for fecal calprotectin.

Data for patients in validation cohort 2 were prospectively gathered from a tertiary referral center located at the University of California San Diego.⁶ (The patient samples from this institution used in the training cohort were distinct from those in the validation cohort.) Among the 195 patients, the median age was 38.5 years (interquartile range, 28-52), and 50.3% were male. All Crohn’s disease locations were represented, including ileal, ileocolonic, and colonic. The AUROC was 0.693 (95% CI, 0.619-0.767) in distinguishing active disease from endoscopic remission. The highest sensitivity, 83.2% (95% CI, 75.0%-89.6%), was seen with an EHI cutoff of 20. Specificity progressively increased as the EHI cutoff rose. At an EHI cutoff of 50, specificity was 87.8% (95% CI, 78.7%-94.0%). At an EHI of 50 or higher, the prevalence of active disease as determined by colonoscopy was 77.3%. With an EHI of less than 20, the prevalence of endoscopic remission was 61.2%. History of a surgery

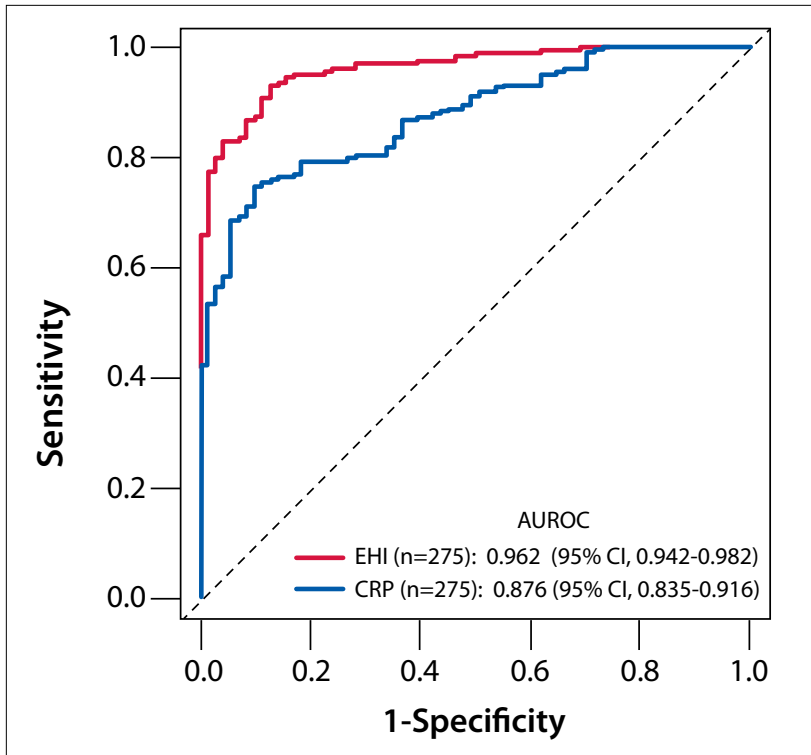


Figure 3. In a report describing the development and validation of the Prometheus Monitr Test, the investigators calculated an AUROC of 0.962 (95% CI, 0.942-0.982) for the EHI and 0.876 (95% CI, 0.835-0.916) for CRP in distinguishing active disease from endoscopic remission. Data for validation cohort 1 are shown. In this cohort, mixed logistic regression models with random intercepts for individual patients were used to combine multiple samples from the same patient. AUROC, area under the receiver operating characteristic curve; CRP, C-reactive protein; EHI, endoscopic healing index. Adapted from D'Haens G et al. *Gastroenterology*. 2020;158(3):515-526.e10.⁶

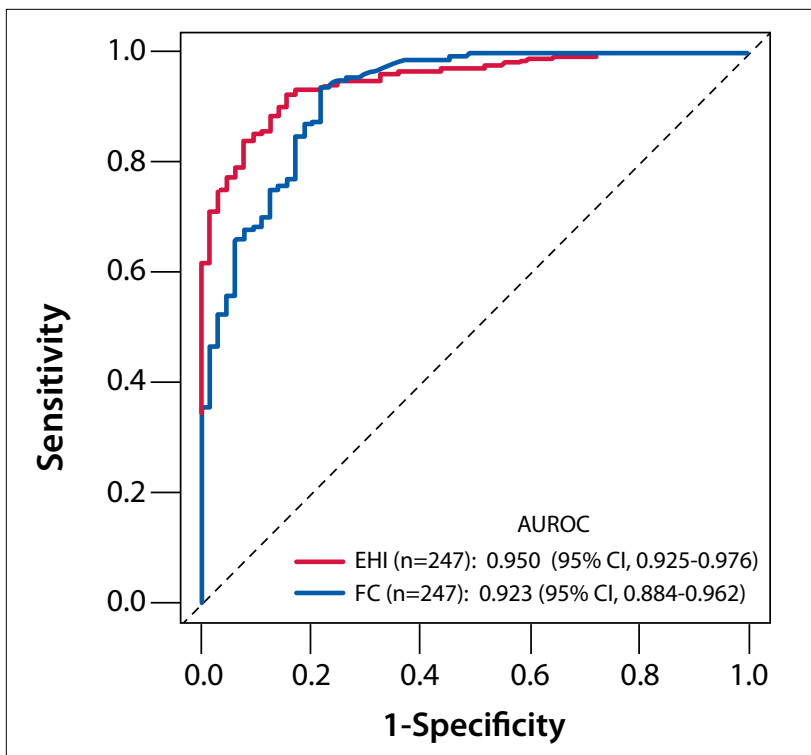


Figure 4. In a report describing the development and validation of the Prometheus Monitr Test, the investigators calculated an AUROC of 0.950 (95% CI, 0.925-0.976) for EHI and 0.923 (95% CI, 0.884-0.962) for fecal calprotectin in distinguishing active disease from endoscopic remission. Data for validation cohort 1 are shown. In this cohort, mixed logistic regression models with random intercepts for individual patients were used to combine multiple samples from the same patient. AUROC, area under the receiver operating characteristic curve; EHI, endoscopic healing index; FC, fecal calprotectin. Adapted from D'Haens G et al. *Gastroenterology*. 2020;158(3):515-526.e10.⁶

related to inflammatory bowel disease (IBD) did not impact the accuracy of the EHI.

D'Haens and colleagues assessed performance of the EHI according to disease location and phenotype.⁶ In both validation cohorts, there were no significant differences for the AUROC of the EHI in distinguishing active disease vs endoscopic remission across disease locations (pairwise $P \geq .171$ and $P \geq .292$, respectively).

In each location, sensitivity and specificity were evaluated at cutoffs observed to have a high performance in both validation cohorts. In validation cohort 1, an EHI cutoff of 20 was associated with a sensitivity of 98.1% (95% CI, 89.7%-100.0%) among patients with L1 (ileal) disease, 100% (95% CI, 88.4%-100.0%) among those with L2 (colonic) disease, and 95.7% (95% CI, 90.1%-98.6%) among those with L3 (ileocolonic) disease. At an EHI cutoff of 50, the specificity was 100%, regardless of the disease location. In validation cohort 2, sensitivity at an EHI cutoff of 20 was 84.6% (95% CI, 65.1%-95.6%) for patients with L1 disease, 78.9% (95% CI, 62.7%-90.4%) for those with L2 disease, and 85.1% (95% CI, 71.7%-93.8%) for those with L3 disease. When using a cutoff of 50, the specificity was 100.0% for L1 disease, 79.3% for L2 disease, and 86.2% for L3 disease. The authors found that the diagnostic accuracy of the EHI was consistent across all disease locations and phenotypes.

Based on these data, D'Haens and colleagues concluded that the EHI score provided by the Prometheus Monitr Test could be used as a noninvasive adjunct for accurately assessing mucosal endoscopic disease activity in patients with Crohn's disease, regardless of the disease location.⁶ An accompanying editorial in *Gastroenterology* noted that the EHI is a promising test that could advance the treat-to-target paradigm.⁷

The Use of the Prometheus Monitr Test in Clinical Practice

In clinical practice, Prometheus Monitr Test is useful for the periodic assessment of endoscopic disease activity, particularly in patients who prefer not to undergo serial colonoscopy to evaluate response to treatment. Administration of the Prometheus Monitr Test could be timed to provide an adjunct assessment of endoscopic disease activity at the beginning of induction, at the end of induction,

and at intervals during maintenance. The test may be used at times in conjunction with colonoscopy—particularly at the beginning of treatment—and in the absence of colonoscopy at later intervals.

The Future Role of the Prometheus Monitr Test

There are many potential roles for the Prometheus Monitr Test in the future. When colonoscopy is not necessary for a visual evaluation, the Prometheus Monitr Test can provide an alternative way to measure the severity of intestinal endoscopic disease activity. Although the Prometheus Monitr Test will not replace colonoscopic assessment, it will add to interval evaluations of patients, a setting in which periodic colonoscopy is not practical. The Prometheus Monitr Test adds a measurement of endoscopic disease activity that can help inform the physician's choice of whether to increase or decrease the treatment dose.⁸

Disclosure

Dr Wolf is a consultant for Prometheus Biosciences.

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Mucosal Healing in Crohn's Disease: Use in Clinical Practice and Recent Data

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Experience With Mucosal Healing in Clinical Practice

Mucosal healing is an important endpoint in the treatment of patients with Crohn's disease. It is associated with reduced surgical procedures, decreased hospitalizations, reduced disability (including decreases in the incidence of cancer and use of corticosteroids), increased quality of life, and possibly a change in the natural history of Crohn's disease.¹⁻³ In the past decade, it has been recognized that mucosal damage can progress even while a patient's symptoms are improving or absent. The disparity between patient-reported symptoms and mucosal healing has been recognized since 1990, when Modigliani published a study of 142 patients with Crohn's disease that showed no correlation between symptoms (as assessed by the CDAI) and the CDEIS.⁴ Only 29% of patients in clinical remission were also in endoscopic remission. Even patients who are asymptomatic can have evidence of active inflammation on endoscopy.⁵ In the past 5 years, the goal for the treatment of Crohn's disease has evolved from managing patient-reported symptoms to the new paradigm of treat to target (T2T), a strategy that involves treating the target of the underlying inflammation.⁶⁻⁸

The target in Crohn's disease was defined by the STRIDE group (Selecting Therapeutic Targets in Inflammatory Bowel Disease) in 2015, as clinical remission (patient-reported outcome) and endoscopic remission. Clinical remission was defined as resolution of abdominal pain and diarrhea/altered bowel habits.⁷ Endoscopic remission in Crohn's disease was defined as resolution of ulcerations at ileocolonoscopy or resolution of findings of inflammation on cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy.

The STRIDE group stressed early control of mucosal inflammation by recommending that the patient undergo reassessment at least every 3 months for re-evaluation of mucosal healing so that adjustments in therapy could be made as needed.⁷

The open-label, phase 3 CALM study (Effect of Tight Control Management on Crohn's Disease) of patients with Crohn's disease compared 2 treatment escalation algorithms: one based on tight control and the other based on clinical management.⁸ The tight control algorithm consisted of clinical symptoms plus biomarkers, such as CRP and fecal calprotectin. The rate of mucosal healing at week 48 was 45.9% in the tight control group vs 30.3% in the clinical management group (95% CI, 3.9%-28.3%; $P=.010$; Figure 5). Mucosal healing was defined as a CDEIS of less than 4 and no deep ulcers 48 weeks after randomization. Key secondary endpoints were also improved with tight control (Figure 6). A long-term analysis showed that patients with endoscopic or deep remission after 1 year of tight control management were less likely to develop disease progression over a median follow-up of 3 years (Figure 7).⁹ Results of the CALM study suggested that noninvasive biomarkers of disease activity can replace endoscopy-based monitoring to help achieve the treatment goal of mucosal healing.⁸

Recent Data on the Clinical Use of the Prometheus Monitr Test

A study by Holmer and colleagues aimed to define the operating characteristics of the EHI in routine clinical practice, with a focus on mucosal ulcers.¹¹ Results were presented at the 2020 Digestive Disease Week (DDW). The EHI was analyzed on serum samples paired with endoscopies obtained from 205 patients with Crohn's disease who participated in a prospective biobank. The study found that EHI scores increased significantly as ulcer size increased ($P<.001$). The sensitivity of an EHI cutoff of 20 points to exclude ulcers of any size was 85% (95% CI, 77%-91%). For ulcers that were large (0.5-20 mm) or very large (>20 mm), sensitivity at this cutoff was 92% (95% CI, 84%-97%). When increasing the EHI cutoff to 50 points, specificity for ruling in any ulcers was 85% (95% CI, 76%-92%) and 87% for large or very large

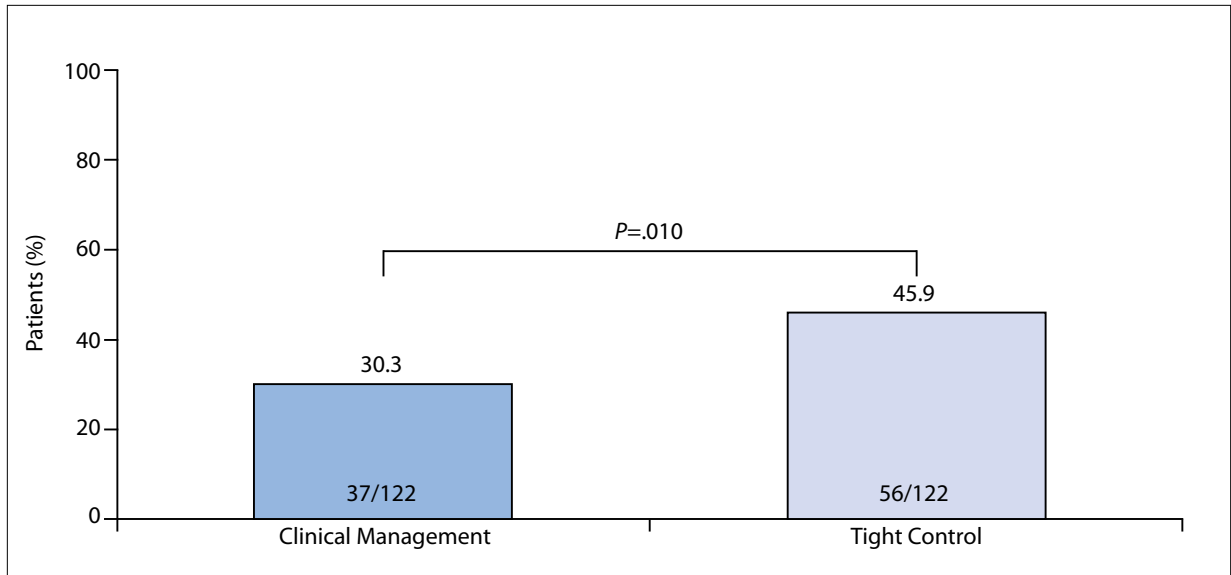


Figure 5. The primary endpoint of mucosal healing at 48 weeks in the open-label, phase 3 CALM study was significantly improved with treatment escalation based on tight control vs clinical management. CALM, Effect of Tight Control Management on Crohn’s Disease. Adapted from Colombel JF et al. *Lancet*. 2018;390(10114):2779-2789.⁸

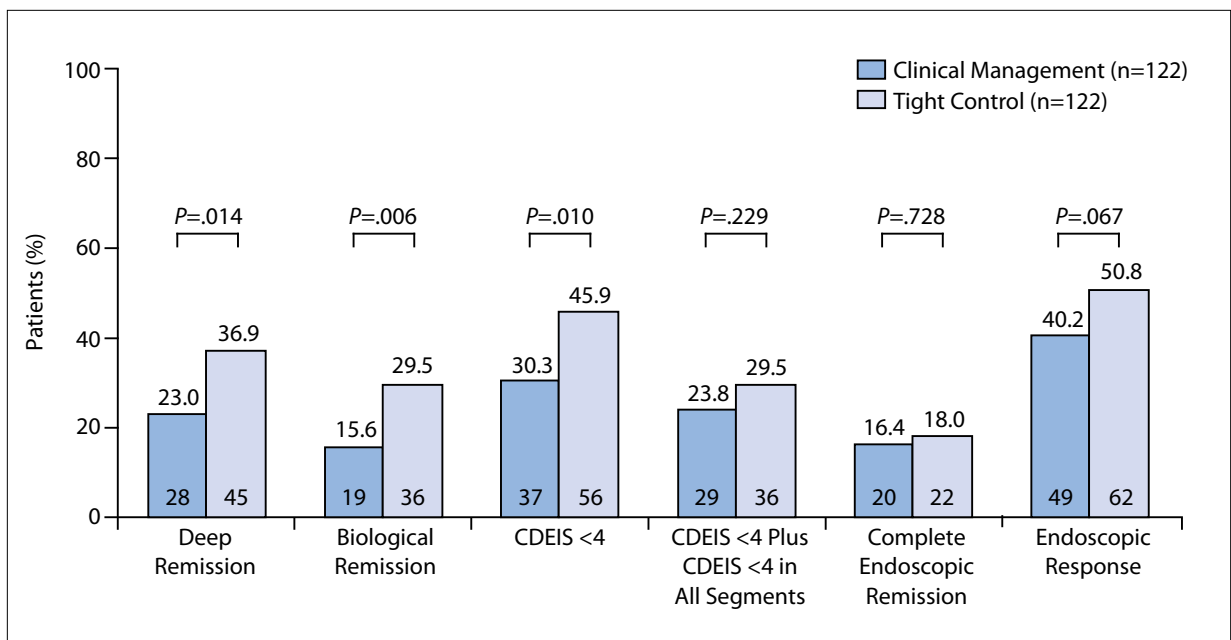


Figure 6. Key secondary endpoints at 48 weeks in the open-label, phase 3 CALM study, which compared treatment escalation based on tight control vs clinical management. CALM, Effect of Tight Control Management on Crohn’s Disease; CDEIS, Crohn’s Disease Endoscopic Index of Severity. Adapted from Colombel JF et al. *Lancet*. 2018;390(10114):2779-2789.⁸

ulcers (95% CI, 79%-92%). The analysis found that each 20-point increase in the EHI score was independently associated with a 1.7-fold increased probability for the presence of large or very large ulcers (adjusted odds ratio, 1.70; 95% CI, 1.13-2.55), after accounting for total

extent of inflamed mucosa, extent of strictured mucosa, and disease location (Figure 8). The researchers concluded that the EHI is significantly higher with increasing endoscopic severity overall, and with individual measures of ulcer size, extent of involvement, and stricture burden.

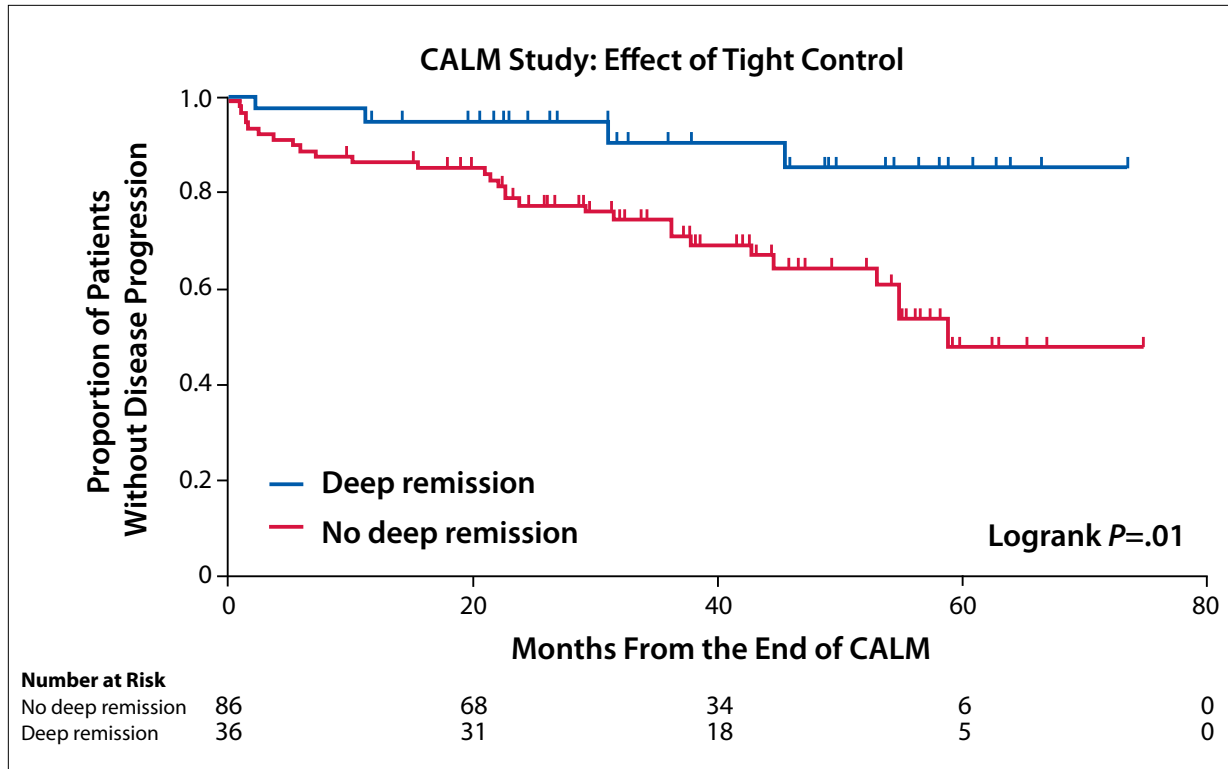


Figure 7. A long-term analysis of the CALM study showed that patients with endoscopic or deep remission after 1 year of tight control management were less likely to develop disease progression over a median follow-up of 3 years. CALM, Effect of Tight Control Management on Crohn's Disease. Adapted from Yzet C et al. ECCO abstract OP35. *J Crohns Colitis*. 2019;13(suppl 1):S024-S025.⁹

This recent study confirmed earlier observations by De Bruyn and colleagues on the usefulness of EHI assessing ulceration in a real-world clinical practice.¹⁰

Other Modalities to Evaluate Mucosal Healing

Endoscopy is considered a gold standard for the assessment of mucosal healing in Crohn's disease, but limitations include cost, risk, and patient compliance.¹²⁻¹⁴ In addition, endoscopy cannot reasonably be performed on a frequent basis (every 3 months). Cross-sectional anatomy imaging studies are sometimes used, but there are limited clinical data available correlating disease activity with bowel healing as observed on imaging (an 85% specificity has been reported).¹⁵ Magnetic resonance imaging and computed tomography are also used.¹⁵

Biomarkers, such as CRP and fecal calprotectin, are used clinically to monitor disease activity.¹⁶ However, there are several limitations to the currently available noninvasive biomarkers. For example, an increased serum level of CRP does not correspond to intestinal inflammation.¹⁶ In addition, 20% to 25% of patients with Crohn's disease are genetically unable to generate an increase in CRP in

response to active inflammation.¹⁷ Therefore, CRP cannot be relied on as an accurate marker of inflammation or disease severity in these patients. In a meta-analysis, the pooled sensitivity and specificity estimates for CRP in patients with IBD were 0.49 (95% CI, 0.34-0.64) and 0.92 (95% CI, 0.72-0.96), respectively.¹⁶

Fecal calprotectin, a breakdown product of inflammatory cells, is a biomarker that can be detected in stool.¹⁸ Like CRP, fecal calprotectin is a measure of inflammation in general, and not mucosal healing specifically.¹⁸ An important limitation to measurement of fecal calprotectin is patient compliance. In my experience, only 50% of patients return their stool sample on first request, and 25% never return the sample at all. Fecal calprotectin is utilized in less than 2% of patients with Crohn's disease in clinical practice.¹⁹ Disease anatomy and location can impact the correlation of fecal calprotectin to endoscopy.²⁰ Measurement of fecal calprotectin levels can vary according to the time of day, the method of analysis, and the stability of the sample.¹⁵ In a meta-analysis, the pooled sensitivity and specificity estimates for fecal calprotectin among patients with Crohn's disease were 0.88 (95% CI, 0.84-0.90) and 0.73 (95% CI, 0.66-0.79), respectively.¹⁶

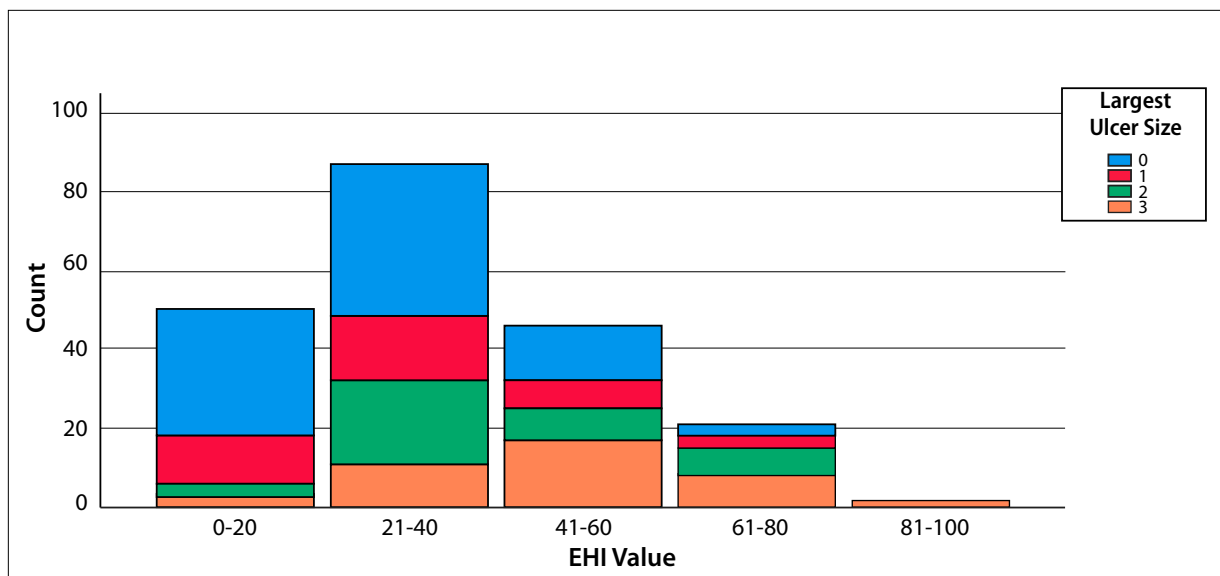


Figure 8. Ulcer size and EHI score in a study that aimed to define the operating characteristics of the EHI in routine clinical practice. EHI, endoscopic healing index. Adapted from Holmer A et al. DDW abstract Su1902. *Gastroenterology*. 2020;158(6 suppl 1):S-694–S-695.¹¹

Use of the Endoscopic Healing Index (EHI) for Monitoring of Disease Activity in Crohn's Disease

A recent experimental *in silico* study by Abreu and colleagues evaluated whether varying the levels of CRP would change the proportion of patients with active disease according to the EHI score.²¹ Simulation data from 8238 patient specimens demonstrated that EHI scores remained relatively stable even when concentrations of CRP were increased. This finding suggests that an isolated increase in CRP does not significantly impact the EHI score or its clinical implications. The authors noted that this finding was not unexpected because the biomarkers included in the EHI algorithm are weighted. They concluded that the algorithm is not dependent on any particular biomarker, but rather reflects all of them. In addition, they stated that the EHI is potentially a reliable, robust alternative for the noninvasive assessment of objective disease activity among patients with Crohn's disease.

Incorporation Into Clinical Practice

Throughout the past 2 years, I have utilized the Prometheus Monitr Test in approximately 250 patients and have found it to be a helpful component of my clinical decision-making. I am a proponent of the treat-to-target strategy. In my practice, I obtain a Prometheus Monitr Test, as well as CRP, fecal calprotectin, and blood work (complete blood count and liver function tests) at initial assessment. I then schedule follow-up visits for every 3

months until remission, then every 6 months as needed, then once a year. Throughout follow-up, these tests are repeated 1 week before the patient's return visit, according to the treat-to-target protocol. In the CALM study, the rate of 1-year remission was 46% with tight control (by including biomarker normalization in addition to clinical remission) vs 30% with a clinical management protocol.⁸

The Future Role of the Prometheus Monitr Test

Treat to target is becoming the preferred method to achieve success in treating Crohn's disease, and possibly in altering the natural history of the disease. Previously, therapeutic adjustments were made reactively, when treatment failed. With the treat-to-target strategy, treatment changes are made proactively, early in the course of the disease.⁸

The successful implementation of treat to target relies on 2 concepts. The first is strict control of active disease and frequent reassessment (every 3 months) with validated biomarkers, until remission is achieved. The second concept is the use of therapeutic drug monitoring to guide changes or adjustments in medications.

At the 2020 DDW meeting, Click and colleagues reported on a cohort of 537 patients who were enrolled in the TARGET-IBD registry (A 5-Year Longitudinal Observational Study of Patients Undergoing Therapy for Inflammatory Bowel Disease).²² The patients underwent a biologic dose change (55.9%) or treatment discontinuation (44.1%) to address lack of efficacy. The

Table 1. Drug Concentrations According to EHI Scores Among Crohn's Disease Patients Treated With Infliximab or Adalimumab in a Retrospective Analysis

Infliximab-Treated Patients (n=261)			
Optimal Serum Anti-TNF Threshold Based on ROC Curve			
	EHI >50	EHI <20	
Drug ≤3.35	68	16	82
Drug >3.35	60	117	179
	128 (49.0%)	133	261
Patients requiring dose escalation: 53.1% (68/128) of EHI >50 26.1% (68/261) of entire cohort			

Adalimumab-Treated Patients (n=398)			
Optimal Serum Anti-TNF Threshold Based on ROC Curve			
	EHI >50	EHI <20	
Drug ≤5.95	111	55	166
Drug >5.95	77	155	232
	188 (47.2%)	210	398
Patients requiring dose escalation: 59.0% (111/188) of EHI >50 27.9% (111/398) of entire cohort			

EHI, endoscopic healing index; ROC, receiver operating characteristic; TNF, tumor necrosis factor. Adapted from Abreu MT et al. DDW abstract 241. *Gastroenterology*. 2020;158(6 suppl 1):S-48.²³

study showed that currently in routine clinical practice, regular assessment of objective disease activity or therapeutic drug monitoring prior to therapeutic management changes is lacking. The reasons for this are unknown, but the authors stressed the importance of such assessments, which may improve biologic positioning and outcomes in IBD.

The combination of using a measure of disease activity (EHI) with therapeutic drug monitoring allows for a better understanding of the reason to increase the treatment dose or change to a different therapeutic agent. At the 2020 DDW Meeting, Abreu and colleagues presented results from a data mining analysis from a commercial clinical laboratory in which EHI was combined with therapeutic drug monitoring to study the association between EHI and serum drug concentrations in adult patients with Crohn's disease treated with anti-tumor necrosis factor (TNF) therapy.²³ The data demonstrated an inverse relationship between EHI and serum concentrations of anti-TNFs. Optimal serum anti-TNF thresholds were identified that best differentiated patients with EHI lower than 20 (indicative of endoscopic remission) vs EHI higher than 50 (indicative of endoscopic active disease). Among patients treated with infliximab,

53.1% of patients with an EHI higher than 50 had serum infliximab concentrations at or less than an optimal threshold of 3.35 µg/mL. These patients would likely benefit from a dose escalation strategy (Table 1). In the future, EHI combined with therapeutic drug monitoring may be helpful in monitoring patients, and longitudinal evaluation could be predictive of future disease escalation.

The addition of EHI as another validated biomarker of disease activity will strengthen the accuracy of detecting disease activity without relying only on expensive and invasive procedures, such as cross-sectional imaging (magnetic resonance enterography) or colonoscopy. Also, I have found EHI to be useful in evaluating and monitoring symptomatic patients with ileal pouch anal anastomosis.

In the current COVID-19 pandemic, endoscopy has not been readily available. Therefore, there is a greater need for biomarkers. Unlike CRP, EHI is stable in the face of infection and can be useful in the management of patients with Crohn's disease.²³

Disclosure

Dr Greenberg is a member of the National Speakers Bureau of Prometheus Biosciences.

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Noninvasive Testing of Mucosal Healing: Current and Future Use in Clinical Practice

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Tools to Assess Mucosal Healing

There are several strategies to monitor disease progression among patients with Crohn's disease. A study evaluated patients' views of disease-monitoring tools.¹ Questionnaires were submitted to more than 900 patients with IBD, including 618 patients with Crohn's disease. Patients with Crohn's disease preferred blood-based tests vs stool-based tests. Colonoscopy was among the least acceptable tests.

A useful tool to assess mucosal healing should have a low false-negative rate and a low false-positive rate. For the EHI score, a threshold of less than 20 minimizes false negatives, and a threshold of 50 or higher minimizes false positives. D'Haens and colleagues compared the utility of CRP, fecal calprotectin, and the EHI score in their article outlining the development and validation of the Prometheus Monitr Test.² In validation cohort 1, the AUROC of the EHI to distinguish active endoscopic disease from endoscopic remission was significantly higher vs CRP alone (EHI, 0.962; 95% CI, 0.942-0.982; CRP, 0.876; 95% CI, 0.835-0.916; $P < .001$). In validation cohort 2, the AUROC of the EHI was numerically better than CRP, but the difference did not reach statistical significance (EHI, 0.693; 95% CI, 0.619-0.767; CRP, 0.624; 95% CI, 0.544-0.704; $P = .109$). In the training cohort, the diagnostic performance of the EHI was significantly better than the AUROC for CRP (EHI vs CRP, 0.748 vs 0.604; $P < .001$). The sensitivity of a CRP cutoff of 5 mg/L ranged from 41.7% (95% CI, 27.6-56.8) to 44.3% (95% CI, 36.9-51.8) in both validation cohorts. The EHI cutoff of 20 had a sensitivity of 91.7% (95% CI, 80.0-97.7) to 96.2% (95% CI, 92.3-98.4).

D'Haens and colleagues noted that patients with Crohn's disease strongly prefer blood-based testing compared with fecal testing.² Currently, however, there are no routinely available blood-based tests with a diagnostic performance comparable to that of fecal calprotectin. The study found similar diagnostic accuracy for EHI and fecal calprotectin in both cohorts. In validation cohort 1, EHI

was numerically superior to fecal calprotectin (EHI vs fecal calprotectin: AUROC, 0.950 vs 0.923; $P = .147$). EHI was numerically inferior to fecal calprotectin in validation cohort 2 (EHI vs fecal calprotectin: AUROC, 0.803 vs 0.854; $P = .298$). Using a cutoff of 50 $\mu\text{g/g}$, the sensitivity of fecal calprotectin was 100% (95% CI, 98.0-100.0) in validation cohort 1 and 75% (95% CI, 60.4-86.4) in validation cohort 2. For an EHI cutoff of 20, sensitivity was 96.2% (95% CI, 92.3-98.4) in validation cohort 1 and 91.7% (95% CI, 80.0-97.7) in validation cohort 2. At a fecal calprotectin cutoff of 250 $\mu\text{g/g}$, specificity was 89.1% (95% CI, 78.8-95.5) in validation cohort 1 and 100% (95% CI, 89.4-100.0) in validation cohort 2. With an EHI cutoff of 50, specificity was 100% (95% CI, 94.4-100.0) in validation cohort 1 and 90.9% (95% CI, 75.7-98.1) in validation cohort 2.

The Prometheus Monitr Test Is Responsive to Changes in Endoscopic Disease Activity

D'Haens and colleagues evaluated use of EHI for monitoring changes in endoscopic disease activity.² Median changes in the EHI score were consistent with endoscopy (SES-CD and CDEIS) and similar to fecal calprotectin (Figure 9). The median effect size of the Prometheus Monitr Test score was significantly better than that of CRP.

The Prometheus Monitr Test and Postoperative Endoscopic Recurrence

Hamilton and colleagues reported on the use of the Prometheus Monitr Test for monitoring mucosal healing in the postoperative setting in patients with Crohn's disease from the POCER (Post-Operative Crohn's Endoscopic Recurrence) clinical trial.^{3,4} The POCER study obtained blood samples at baseline and then at 6, 12, and 18 months postoperatively. A total of 132 patients were included (46.2% male; median age, 36.2 years), providing 439 samples for assessment. The median duration of

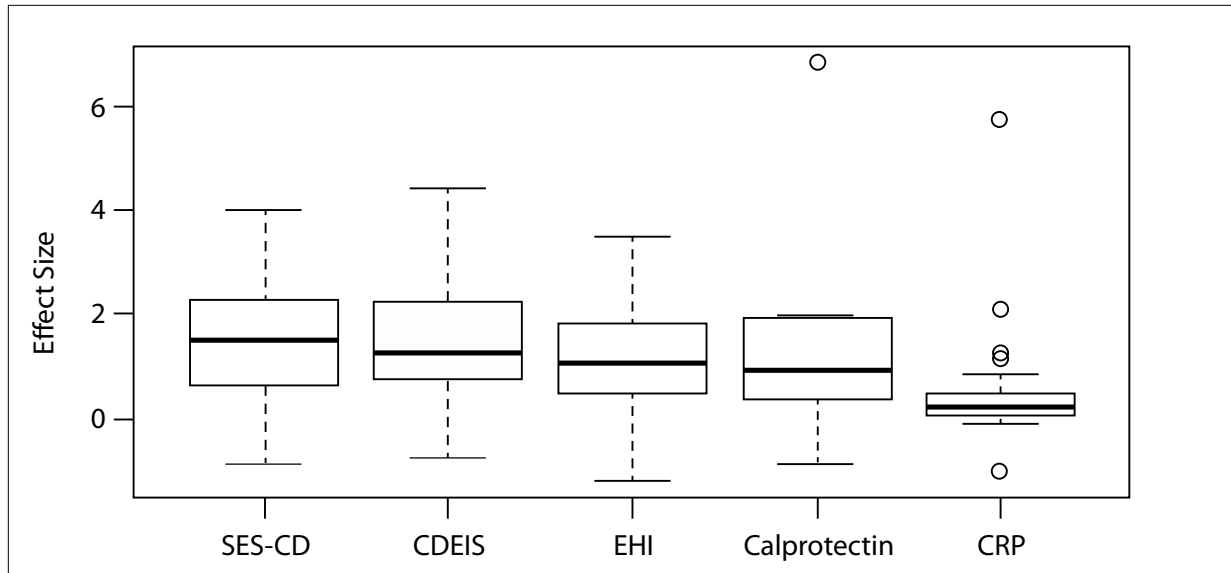


Figure 9. In a report describing the development and validation of the Prometheus Monitr Test, the median changes in the EHI score were consistent with endoscopy (SES-CD and CDEIS) and similar to fecal calprotectin. Scores are shown for assessments made between baseline and week 12 (n=70). CDEIS, Crohn's Disease Endoscopic Index of Severity; CRP, C-reactive protein; EHI, endoscopic healing index; SES-CD, Simple Endoscopic Score for Crohn's Disease. Adapted from D'Haens G et al. *Gastroenterology*. 2020;158(3):515-526.e10.²

disease was 9 years. At baseline, the median EHI score was significantly different according to the indication for surgery. The median EHI scores were 23 for surgery after treatment failure, 39 for surgery to treat obstruction, and 46 for surgery to treat perforation ($P=.007$).

This study showed a statistically significant change in the median EHI across all time points ($P=.0001$), with a precipitous decrease in the median EHI between baseline and 6 months postoperatively (median EHI, 39.1 at baseline vs 25.6 at 6 months; $P<.001$).⁴ There were no significant differences in the EHI according to medication use at 6 or 18 months. The median EHI was 22.2 among patients with normal mucosa at 18 months vs 33.7 among patients with a severe recurrence at this time, a significant difference ($P=.004$).

The AUROC for the discrimination between mucosal normality and severe recurrence was 0.75 (95% CI, 0.64-0.87). The POCER investigators concluded that the EHI score was sufficiently accurate to have clinical utility as an adjunctive test for monitoring postoperative recurrences in patients with Crohn's disease.

The Relationship Between the Endoscopic Healing Index (EHI) and Serum Concentrations of Anti-TNFs in Patients With Crohn's Disease

Abreu and colleagues evaluated the correlation between EHI and anti-TNF concentrations to identify patients who might benefit from dose escalation.⁵ Results were presented at the 2020 DDW meeting. This retrospective

analysis included patients with Crohn's disease who had received infliximab (n=591) or adalimumab (n=853). The study identified a linear inverse relationship between median EHI scores across infliximab and adalimumab concentration quartiles ($P<.0001$ for both). The median EHI was higher among patients with anti-TNF antibodies (Figure 10). Receiver operating characteristic (ROC) curves identified thresholds associated with EHI scores of less than 20 for infliximab concentrations above 3.45 $\mu\text{g}/\text{mL}$ (area under curve [AUC], 0.702; sensitivity, 53.1%; specificity, 88.0%) and for adalimumab concentrations above 5.95 $\mu\text{g}/\text{mL}$ (AUC, 0.682; sensitivity, 59.0%; specificity, 73.8%). In the infliximab cohort, 49% of patients (128 of 261) had an EHI score higher than 50. Among these patients, 53.1% (68 of 128) had an infliximab concentration at or below 3.45 $\mu\text{g}/\text{mL}$ and could benefit from dose escalation. In the adalimumab cohort, 47.2% of patients (188/398) had an EHI score higher than 50. Among these patients, 59% (111/188) had an adalimumab concentration of 5.95 $\mu\text{g}/\text{mL}$ or lower, indicating a need for dose escalation. Abreu and colleagues concluded that serum anti-TNF drug concentrations combined with EHI scores could identify patients who may require dose modification.

The Use of the Prometheus Monitr Test in Clinical Practice

I use the Prometheus Monitr Test in clinical practice in 2 situations: (1) to monitor response to therapy during treatment of Crohn's disease and (2) to assess for postop-

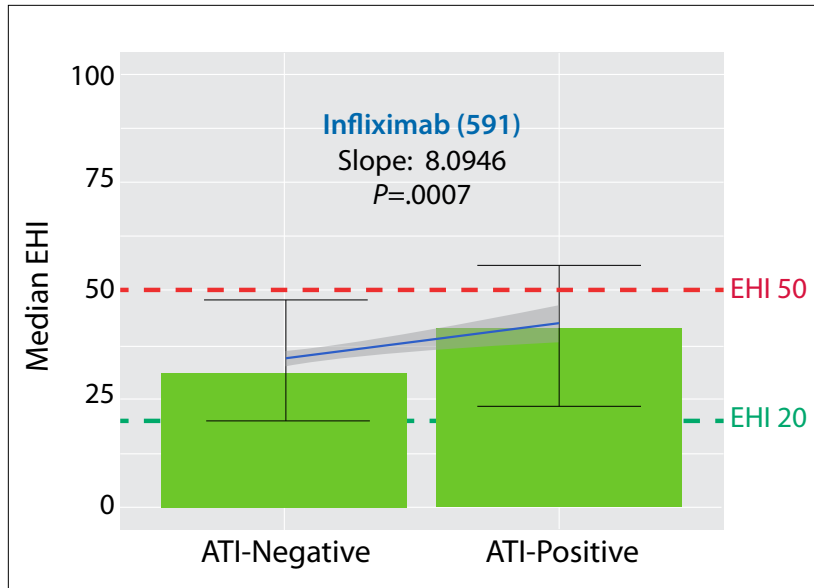


Figure 10. In a retrospective analysis, the median EHI was higher among patients treated with infliximab who had anti-TNF antibodies. ATI, antibodies to infliximab; EHI, endoscopic healing index. Adapted from Abreu MT et al. DDW abstract 241. *Gastroenterology*. 2020;158(6 suppl 1):S-48.⁵

erative recurrence of Crohn's disease. When patients with Crohn's disease respond to biologic therapy and their EHI decreases to less than 20, I am confident that mucosal healing has been achieved (and sustained). In these patients, I will then administer the Prometheus Monitr Test every 6 months to assess maintenance of remission. I administer the test sooner if symptoms change, to assess Crohn's disease recurrence. In the postoperative setting, the Prometheus Monitr Test is uniquely positioned, and testing every 6 months is reasonable. The majority of my patients achieve a low level EHI (<20) after an intestinal resection. Although I still perform colonoscopy 6 months after surgery, I also administer the Prometheus Monitr Test. I have found a correlation between an unchanged, low EHI score and colonoscopic remission. For patients with an EHI of less than 20 that subsequently increases over time, I will perform a colonoscopy sooner to assess for postoperative recurrence of Crohn's disease.

The Future Role of the Prometheus Monitr Test

These data raise the question of how the Prometheus Monitr Test will be incorporated into the postoperative management of patients with Crohn's disease. The primary implication for clinical practice is that the Prometheus Monitr Test may provide a noninvasive method to routinely assess patients in the postoperative setting. For example, it might be used in a patient who has undergone an ileocecal resection. In such a patient, the EHI score on the Prometheus Monitr Test would be highly elevated prior to surgery. Subsequent Prometheus Monitr Tests could then serve as a noninvasive monitor for disease recurrence. The Prometheus Monitr Test may

also help guide the optimization or timing of postoperative biologic therapy. Importantly, the Prometheus Monitr Test may provide the opportunity to intervene at an earlier time point.

The Prometheus Monitr Test could provide a more accurate determination of which patients have disease recurrence. The test can provide a better indication for when colonoscopy is required vs when the procedure could be delayed. The Prometheus Monitr Test has the potential to optimize postoperative management to prevent recurrence and guide treatment decisions. Ultimately, the test might be used to avoid unnecessary surgery.

Disclosure

Dr Regueiro is an advisory board member and/or a consultant for AbbVie, Janssen, UCB, Takeda, Pfizer, Miraca Labs, Amgen, Celgene, Seres, Allergan, Genentech, Gilead, Salix, Prometheus Biosciences, Lilly, and TARGET PharmaSolutions.

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Optimizing Strategies to Assess Mucosal Healing in Patients With Crohn's Disease: Discussion

Miguel D. Regueiro, MD, Douglas C. Wolf, MD, and Eugene Greenberg, MD, FACP, FACC, AGAF

Miguel D. Regueiro, MD Mucosal healing is a clinical target and an important endpoint in the treatment of patients with IBD.¹⁻⁴ However, we clearly need better modalities to evaluate mucosal inflammation and to assess mucosal healing. The utility of endoscopy is limited in this setting.¹ As we aim toward a target based on histology, clinicians are interested in identifying better biomarkers and ways to stratify patients based on responses that are less subjective than the endoscopic scoring systems used today.

Douglas C. Wolf, MD No patient likes to undergo repeated colonoscopies. It is a difficult procedure that is potentially expensive.⁵ Identification of noninvasive measures that correlate well with visual endoscopic healing will have an important role in patient management. The biomarkers, for example, in use today have limitations.⁷ A colonoscopy with biopsies that are normal, with no evidence of inflammation, may conflict with a biomarker test. For example, the patient may have elevated levels of fecal calprotectin or CRP. Therefore, there may not be any one test—even a colonoscopy—that will be a perfect indicator of exactly what is occurring in the gut mucosa. As we do our best to hit the target of deep remission, including mucosal remission, different tests that may offer similar or complementary feedback will prove useful.

Miguel D. Regueiro, MD Among postoperative Crohn's disease patients—those who had surgery with pouches or an ileocolonic anastomosis—the EHI may be a good way to predict recurrence, and also to help guide response to different treatments. For those patients who maintain a low EHI (<20), the likelihood of postoperative recurrence could be low. Continuing their current treatment strategy may be reasonable.

Eugene Greenberg, MD I treated a patient with an EHI of 61, who also had a high fecal calprotectin level. She proceeded to surgery because of stricture and active disease. I usually perform colonoscopy 6 months postoperatively in order to evaluate patients for early recur-

rence or residual disease in order to formulate a plan for postoperative therapy. In this case, because of concern for early recurrence in aggressive disease, I checked fecal calprotectin and EHI at 2 months postoperative and again at 3 months postoperative. The results of EHI at 2 and 3 months postoperative were 22 and 35, respectively. This suggests that EHI normalizes rapidly after surgery and therefore could be repeated at 3 months to assess recurrence based on the longitudinal increase in EHI levels. An abnormal EHI could be confirmed with colonoscopy, and allow earlier therapeutic intervention.

I have also found EHI in combination with fecal calprotectin to be helpful in the evaluation of patients with ileal pouch–anal anastomosis who are symptomatic.

Another point to mention is that approximately half of my patients do not return a stool sample for fecal calprotectin testing. After I remind them that the alternative is a colonoscopy, another quarter will comply. Overall, however, approximately 25% of my patients never drop off the stool sample for fecal calprotectin testing.

Miguel D. Regueiro, MD In my practice, adherence to the fecal calprotectin test is not good. Coupled with issues with the test itself, it is almost becoming a useless modality since many of my patients will refuse the stool test. This is where I think having a blood test—which patients do not seem to mind as much—will provide better adherence and utility in the clinic.

Douglas C. Wolf, MD Levels of CRP, lactoferrin, and fecal calprotectin may not be informative.⁶ In some cases, there is clear inflammation at colonoscopy, but the results of these tests are normal. As mentioned, some patients may wish to avoid or delay colonoscopy. There clearly is a need for another test that may complement those others and may, in a subgroup of patients, provide a better measure of inflammation. The Prometheus Monitr Test is especially useful in the subgroup of patients with normal CRP and normal stool biomarkers, as it provides an alternate measure of inflammation that is complementary to, but distinctive from, these standard biomarkers. It is well-

known that a subgroup of patients with active inflammation at colonoscopy are not accurately assessed with standard biomarker testing. In these patients, the Prometheus Monitr Test would be uniquely positioned to provide a noninvasive inflammation test for initial assessment and for serial monitoring. Results would add another dimension to the evaluation beyond that provided by CRP and the stool biomarkers.

Disclosure

Dr Wolf is a consultant for Prometheus Biosciences. Dr Greenberg is a member of the National Speakers Bureau of Prometheus Biosciences. Dr Regueiro is an advisory board member and/or a consultant for AbbVie, Janssen, UCB, Takeda, Pfizer, Miraca Labs, Amgen, Celgene, Seres, Allergan, Genentech, Gilead, Salix, Prometheus Biosciences, Lilly, and TARGET PharmaSolutions.

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Slide Library

The Role of Mucosal Healing in Crohn's Disease

- Mucosal healing has become an important clinical target for patients with Crohn's disease¹
- Mucosal healing correlates with^{2,4}:
 - Reduced need for surgery
 - Reduced need for hospitalization
 - Maintenance of a high quality of life

1. Bouquern G et al. *Gastrointestinal Hepatol*. 2015;13(8):1642-1656. 2. D'Onofrio T, Ciccarelli F. *Gastroenterol*. 2014;127:1511-1515. 3. Lichtenstein GR et al. *Am J Gastroenterol*. 2009;114(2):405-415. 4. Chikara S et al. *Aliment Pharmacol Ther*. 2011;35(10):1211-1222.

Mucosal Damage in Crohn's Disease

- Mucosal damage can progress even while a patient's symptoms are improving or absent¹
- Patients who are asymptomatic can have evidence of active inflammation on endoscopy²
- In the past 5 years, the goal for the treatment of Crohn's disease has evolved from managing patient-reported symptoms to the paradigm of treat to target (T2T), a strategy that involves treating the target of the underlying inflammation³⁻⁵

1. Meddings B et al. *Gastroenterology*. 1993;104(4):1140-1145. 2. Baumert W et al. *Inflamm Bowel Dis*. 2011;17(11):2244-2250. 3. Bouquern G et al. *Gastroenterol Hepatol*. 2015;13(8):1642-1656. 4. Lichtenstein GR et al. *Am J Gastroenterol*. 2009;114(2):405-415. 5. Chikara S et al. *Aliment Pharmacol Ther*. 2011;35(10):1211-1222.

Treat to Target

- Treat to target has become the preferred method to achieve success in treating Crohn's disease
- With the treat-to-target strategy, treatment changes are made proactively, early in the course of the disease
- The successful implementation of treat to target relies on 2 concepts:
 - Strict control of active disease and frequent reassessment (every 3 months) with validated biomarkers, until remission is achieved
 - The use of therapeutic drug monitoring to guide changes or adjustments in medications

Limitations to the Use of Colonoscopy to Measure Mucosal Healing

- Colonoscopy is the gold standard for measuring mucosal healing, but has several limitations:
 - Variations in bowel preparation quality
 - The need for serial examinations to compare degrees of endoscopic disease activity
 - The procedure's relative invasiveness

The CALM Study in Crohn's Disease

- The open-label, phase 3 CALM study compared 2 treatment escalation algorithms: one based on tight control and the other based on clinical management
- The tight control algorithm consisted of clinical symptoms plus biomarkers, such as CRP and fecal calprotectin
- The rate of endoscopic remission at week 48 was 45.9% in the tight control group vs 30.3% in the clinical management group (95% CI, 3.9%-28.3%; $P < .010$)¹
- In a long-term analysis, patients with endoscopic or deep remission after 1 year of tight control management were less likely to develop disease progression over a median follow-up of 3 years²
- These results suggest that noninvasive biomarkers of disease activity can replace endoscopy-based monitoring to help achieve mucosal healing¹

CALM Effect of Tight Control Management on Crohn's Disease. CRP, C-reactive protein. 1. Cosmes J et al. *Lancet*. 2018;391(10116):2279-2289. 2. Cosmes J et al. *Gastroenterology*. 2019;156(1):100-110.

Measurement of Mucosal Healing: The Prometheus Monitr Test

- The Prometheus Monitr Test consists of 13 biomarkers that represent 6 biologic pathways involved in the process of mucosal healing and mucosal homeostasis
- Biomarkers include those from the angiotensin and matrix metalloproteinases families, as well as carcinoembryonic antigen-related cell adhesion molecule 1, C-reactive protein, serum amyloid A1, interleukin 7, transforming growth factor α , vascular cell adhesion molecule 1, and extracellular matrix metalloproteinase inducer
- The test provides a score known as the endoscopic healing index (EHI)

The Endoscopic Healing Index (EHI)

- The EHI score is graded on a scale of 0 to 100, from low risk to high risk
- Information regarding the development and validation of the EHI model and the Prometheus Monitr Test was published in 2020
- At a cutoff score of 20, the sensitivity of the EHI was 83.2% for excluding endoscopically active disease, with a specificity of 36.6%
- At a cutoff score of 50, the sensitivity of EHI was 30.1% for excluding endoscopically active disease, with a specificity of 87.8%
- For EHI cutoffs of at least 20 but less than 50, specificity steadily increased as the scores approached 50, which indicates a higher likelihood of active disease

©Harris et al. Gastroenterology. 2020;158(3):510-526.e18.

The POCER Study

- The prospective POCER study evaluated the use of the Monitr test for monitoring mucosal healing in the postoperative setting in Crohn's disease
- Blood samples were obtained from 132 patients at baseline and at 6, 12, and 18 months postoperatively
- There was a statistically significant change in the median EHI across all time points ($P<.0001$), with a precipitous decrease between baseline and 6 months postoperatively (median EHI, 39.1 at baseline vs 25.6 at 6 months; $P<.001$)
- The median EHI was 22.2 among patients with normal mucosa at 18 months vs 33.7 among patients with a severe recurrence at this time ($P=.004$)
- The investigators concluded that the EHI score was sufficiently accurate to have clinical utility as an adjunctive test for monitoring postoperative recurrences

POCER. Post-Operative Crohn's Endoscopic Recurrence. Hamilton et al. EHE abstract #01799. Gastroenterology. 2019;156(suppl 1):S-943.

The Prometheus Monitr Test in Clinical Practice

- In clinical practice, the Prometheus Monitr Test is useful for the periodic assessment of endoscopic disease activity, particularly in patients who prefer not to undergo serial colonoscopy to evaluate response to treatment
- Administration of the test could be timed to provide an adjunct assessment of endoscopic disease activity at the beginning of induction, at the end of induction, and at intervals during maintenance
- The test may be used at times in conjunction with colonoscopy—particularly at the beginning of treatment—and in the absence of colonoscopy at later intervals

The Future Role of the Prometheus Monitr Test

- When colonoscopy is not necessary for a visual evaluation, the Prometheus Monitr Test can provide an alternative way to measure the severity of intestinal endoscopic disease activity
- The test will add to interval evaluations of patients, a setting in which periodic colonoscopy is not practical
- The test may provide a noninvasive method to routinely assess patients in the postoperative setting
- The test has the potential to optimize postoperative management to prevent recurrence and guide treatment decisions

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